Genetic variants and risk of chronic kidney disease

Devuyst, Olivier

DOI: https://doi.org/10.3747/pdi.2014.00063

Genetic Variants and Risk of Chronic Kidney Disease

Genetic factors are increasingly recognized to contribute to the risk of chronic kidney disease, and important differences in the risk of progression to end-stage renal disease have been observed in different racial groups (1). In particular, African American patients have 4- to 5-fold more kidney failure than white patients. Identifying genetic factors contributing to this increased risk is of major importance to address renal disease progression (2).

Seminal investigations led by Martin Pollak and colleagues have shown that a locus on chromosome 22 (22q.13) accounts for the essential of the increased risk of end-stage renal disease in black patients. The risk is associated with two variants in the *APOL1* gene that encodes apolipoprotein L1 (ApoL1), which is part of a circulating protein complex that can lyse *Trypanosoma brucei* and other trypanosomes responsible for the African sleeping sickness. While humans are resistant to *T. brucei* because of ApoL1, a virulent subspecies (*T. brucei rhodesiense*) has emerged, that is resistant to ApoL1-mediated lysis. The two variants of *APOL1*, called G1 and G2, confer protection against potentially lethal infections by *T. brucei rhodesiense*, explaining why they are frequent in populations of recent African descent (2). In fact, about 50% of African Americans having either one or two *APOL1* G1 or G2 risk alleles.

Recently, Parsa et al. have extended the *APOL1* paradigm, by examining the effect of the G1 and G2 variants of *APOL1* on the progression of chronic kidney disease in two prospective, multicenter studies involving patients with chronic kidney disease: the African American Study of Kidney Disease and Hypertension (AASK, 693 patients) and the Chronic Renal Insufficiency Cohort (CRIC, 2955 patients) (3). The high-risk group was defined as having 2 copies of high risk variants, whereas the low-risk group had 0 or 1 copy. A consistent and robust association between the presence of *APOL1* risk variants and higher rates of end-stage renal disease and progression of chronic kidney disease was observed in black patients as compared with white patients, regardless of diabetes status. In the AASK study for instance, patients with 2 copies of *APOL1* risk variants were twice as likely to progress to the composite of end-satge renal disease or a reduction of 50% in the eGFR from baseline over a median follow-up of 9 years. Of note, the progression of CKD was not influenced by blood pressure control (as compared to the *APOL1* status), and there was no interaction between the *APOL1* genotype and treatment with an ACE inhibitor in the black population.

These studies confirm the robust association of renal risk variants in *APOL1* with higher rates of end-stage renal disease and progression of chronic non-diabetic kidney disease in black patients as compared with white patients. They also demonstrate that, in a context of recent selection pressure against pathogens in African Americans, a risk variant that is relatively frequent may also have a large effect size (2). Future research will need to address the mechanism by which ApoL1 cause renal disease (we only known that ApoL1 is expressed in the glomerulus), as well as the inconsistent effect of *APOL1* genotype in patients with diabetic kidney disease.

AU: Olivier Devuyst

Disclosure: None

References:

1. Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Köttgen A, Levey AS, Levin A. Evolving importance of kidney disease: from subspecialty to global health burden. Lancet. 2013 Jul 13;382(9887):158-69.

2. Friedman DJ, Pollak MR. Genetics of kidney failure and the evolving story of APOL1. J Clin Invest. 2011 Sep;121(9):3367-74.

3. Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, Feldman HI, Parekh RS, Kusek JW, Greene TH, Fink JC, Anderson AH, Choi MJ, Wright JT Jr, Lash JP, Freedman BI, Ojo A, Winkler CA, Raj DS, Kopp JB, He J, Jensvold NG, Tao K, Lipkowitz MS, Appel LJ; AASK Study Investigators; CRIC Study Investigators. APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013 Dec 5;369(23):2183-96.

Correspondence: Prof. Dr. Olivier Devuyst, Institute of Physiology, University of Zurich.

E-mail: olivier.devuyst@uzh.ch